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# Asymmetric Synthesis in Simmons-Smith Reaction\*

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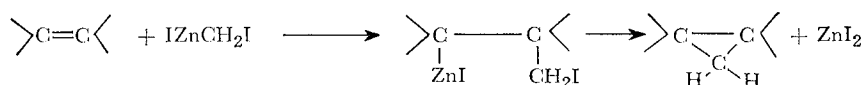
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A new general stereospecific synthesis of cyclopropanes which involved the treatment of olefins with an active intermediate, iodomethylzinc iodide, prepared from methylene iodide and zinc-copper couple has been developed by Simmons and Smith<sup>1)</sup>, and has been proved very useful in preparative applications.

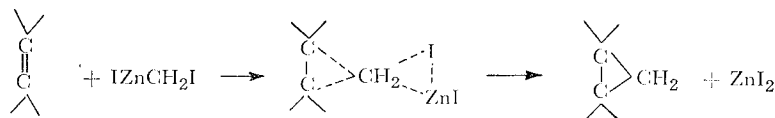
Wittig introduced an alternative method for generation of iodomethylzinc iodide, namely addition of a solution of diazomethane to an ethereal solution of zinc iodide and olefin<sup>2)</sup>.

As to mechanism of Simmons-Smith reaction, Hoberg<sup>3)</sup> postulated the cyclopropane formation as proceeding via addition of the active intermediate iodomethylzinc iodide to olefin and subsequent elimination of zinc iodide:



Since the cyclopropane formation in this reaction is stereospecific, this two-step mechanism implies a well-defined stereochemistry in both the addition and the elimination steps, as well as configurational stability of the organozinc intermediate, but neither of these requirements seems not to have been substantiated.

In an alternative, a three-center reaction involving a one-step displacement of zinc iodide from iodomethylzinc iodide by olefin, *i.e.* a methylene transfer mechanism has been presented<sup>1a, 1c, 2b, 4)</sup>.



In connection with this unresolved mechanistic problem, it seemed of interest to undertake asymmetric synthesis in Simmons-Smith reaction as a possible means of mechanistic solution.

We wish, at this time, to report some preliminary results of asymmetric synthesis in Simmons-Smith reaction.

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Table 1.

Substrate	Product	b.p. (°/mm)	$n_D^{25}$	% Yield	$[\alpha]_D^{25}$ (chl.f.)	Absolute configuration
(-)-Menthyl crotonate	2-Methylcyclopropanecarboxylic acid	98-100/18	1.4374	14 17.5 21	+1.47 +0.74 +1.82	(1S:2S) <sup>6)</sup>
(-)-Menthyl senecioate	2,2-Dimethylcyclopropanecarboxylic acid	96-96.5/17	1.4390	16.5	+ 6.6 + 7.2	(S?) <sup>a)</sup>
(-)-Menthyl fumarate	<i>trans</i> -1, 2-Cyclopropanedicarboxylic acid <sup>b)</sup>	96-99/15.5	1.4420	14.8	+12.8 +12.3 <sup>c)</sup>	(1S:2S) <sup>8)</sup>
(-)-Menthyl cinnamate	<i>trans</i> -2-Phenylcyclopropanecarboxylic acid <sup>b)</sup>	126-7.5/9.5	1.5284	33.5 27 26	-29.3 -29.1 <sup>c)</sup> -27.3 - 8.5	(1R:2R) <sup>8,9)</sup>

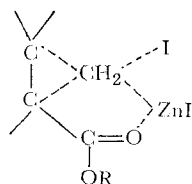
a) Predicted by Brewster calculation of conformational asymmetry<sup>7)</sup>.

b) The product acid was converted into methyl ester by standard method with diazomethane.

c) Values in ethanol.

With a molar ratio of olefinic ester: methylene iodide: zinc-copper couple<sup>5)</sup> of 1:2:2 in absolute ether and a reflux period of 60 hours, (-)-menthyl  $\alpha$ ,  $\beta$ -unsaturated esters afforded the corresponding cyclopropane compounds, which were isolated pure from the reaction mixture by the usual work-up, ozonolysis to remove unreacted olefinic esters and subsequent hydrolysis. The identity of products was obtained by elemental analysis, IR-spectrum comparison and vapor phase chromatography.

As is seen from the tabulated data, all the (-)-menthyl esters except cinnamate when treated with Simmons-Smith reagent, afforded (+)-(1S:2S)-acids in contrast to what was expected from the Cram-Prelog model. It may be considered that the addition did occur in a two-step fashion as Hoberg postulated, but the steric course was altered by the presence of catalytic amount of copper as was experienced in the case of conjugate addition of Grignard reagent to  $\alpha$ ,  $\beta$ -unsaturated ester<sup>10)</sup>. Alternatively, the one-step methylene transfer mechanism through a transition intermediate involving simultaneous coordination of zinc of the reagent with ester carbonyl oxygen, which necessitates a twisted cisoidal conformation of  $\alpha$ ,  $\beta$ -unsaturated ester in order to form (3.1,0)-bicyclic, should naturally lead to the formation of (+)-(1S:2S)-cyclopropane products.



It may appear contradictory to postulate such a cyclic intermediate involving

metal coordination in this case while denying the similar cyclic concerted mechanism in another<sup>10)</sup>, but the electrophilic character and the more covalent carbon-metal bond of Simmons-Smith reagent in contrast to the nucleophilic character and the more ionic character of carbon-magnesium bond in Grignard reagent may account for the difference in their reactivity.

Actually, accelerating and directing influence of oxygen functions such as hydroxyl and ether on the steric course of addition was pointed out in some cases<sup>1a, 11), 12)</sup> and it has been proved that in reactions of olefinic alcohols, transfer of methylene occurs intramolecularly via an intermediate zincate so that the addition is only possible from the side of the double bond nearest the oxygen atom<sup>13)</sup>.

In order to test the working hypothesis, (-)-menthyl *trans*-3-pentenoate was subjected to the same reaction. In this system, the ethylenic bond is removed by one methylene from carbomethoxy group, which favors the electrophilic addition of the reagent and at the same time, enables the suspected zinc-oxygen coordination more easily to form in a less strained (4.1.0)-bicyclic transition intermediate complex. Consistently, a better reaction yield (54.4%) and a greater rotation (+1.6°, neat) of the cyclopropane product were obtained. Another evidence in support of the one-step mechanism via an intermediate complex was obtained in an asymmetric synthesis of (-)-*trans*-2-methylcyclopropanecarboxylic acid by treating methyl crotonate with Simmons-Smith reagent in the presence of (-)-menthol. A prior complex formation or reaction of the reagent with hydroxyl of (-)-menthol and not with carboxyl oxygen, and subsequent methylene transfer from (-)-menthyl zincate or complex by methyl crotonate may reasonably account for this asymmetric synthesis.

In the exceptional case of (-)-menthyl cinnamate, the conjugation of phenyl group in this system enhances the nucleophilicity of ester carbonyl oxygen and effects the coordination of zinc, but at the same time, the partial double bond character of the single bond between carboxyl carbon and  $\alpha$ -carbon acquired by the conjugation of  $\alpha$ ,  $\beta$ -double bond is enhanced by further conjugation of phenyl. This higher delocalization energy barrier inhibits the deviation from the transoidal coplanarity of the conjugated system to attain a twisted cisoidal (3.1.0)-bicyclic transition intermediate complex. Then, another molecule of the reagent attacks the double bond of cinnamate already complexed with the reagent at the oxygen, and the methylene transfer takes place in the less hindered side of the transoidal coplanar (-)-menthyl cinnamate, thus leading to the formation of (-)-(1*R*;2*R*)-acid.

Studies to substantiate the working hypothesis are currently in progress and will be published elsewhere in details.

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